REMARKS

Reconsideration of the application in view of both the above amendment and the following remarks is requested.

The Objection to the Abstract

The Abstract has been objected to for its failure to coincide with the claimed invention. Specifically, the Examiner takes issue with the disparity between the chemical nomenclature used in the abstract and the chemical nomenclature used in the claims. Both the claims and the abstract are herein amended to clarify the earlier mistakes in chemical nomenclature. The Examiner takes further issue with the abstract's disclosure of the prevention of both the development of antibiotic drug resistance and bacteria-to-bacteria transfer of genes. More specifically, the Examiner appears to take exception to such disclosure while Applicant *claims* methods drawn to the reduction of the adherence of microorganisms to epithelial cells. "The purpose of the abstract is to enable the United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the *technical disclosure*. The abstract will not be used for interpreting the scope of the claims." 37 C.F.R. §1.72 (b) (emphasis added). As the material objected to is both important *to*, and fully supported *by*, the specification *as filed*, Applicant has opted to add reference to the claims rather than make deletions of this material. The herein newly-submitted *Abstract of the Disclosure* is now wholly directed toward Rule 1.72(b)'s aspiration of providing that fully informative encapsulation of the *technical disclosure*.

The Objection to the Disclosure

The disclosure has been objected to because of disagreement over the formal nomenclature of taurolidine. More specifically the disagreement lies in whether taurolidine contains a 1,1 dioxide functionality or a 1,2 dioxide functionality. Applicant hereby agrees with the Examiner's position that taurolidine is indeed 1,1 dioxo functionalized, and has amended his abstract and specification accordingly. In response to the Examiner's request for the structure, Applicant submits that 4,4'-methylenebis(tetrahydro-1,2,4 thiadiazine-1,1-dioxide)—an element of the claims—is the proper IUPAC[1] nomenclature from which any chemist of ordinary skill could readily derive the structure of Applicant's intended compound. *Yet*, Applicant *would* direct the Examiner's attention to the structural illustration on page 2 of the *provisional* parent application filed September 11, 1997, identified by U.S.S.N. 60/058,497.

The Rejection of Claims 7-12 under 35 U.S.C. §112, 1st ¶

Claims 7-12 have been rejected under 35 U.S.C. §112, first paragraph, *ostensibly* for the disclosure's failure provide a written description, and *expressly* for the introduction of new matter. Specifically, the rejection states that there is no support in the specification for claims directed to a method of reducing the adherence of microorganisms to epithelial cells. Moreover, the rejection admonishes that 'the term "epithelial cells" appears not to have been mentioned in the specification.' Applicant

[1] The IUPAC (International Union of Pure and Applied Chemistry) system of organic nomenclature was developed by various committees and commissions of chemists from all over the world. This Union of world chemists and its efforts to bring uniformity to organic nomenclature dates back to 1892.

disagrees with both of these contentions and would call the Examiner's attention to the following selection excerpted from the instant specification.

> "Microbial adherence to mucosal ***epithelial cells*** is recognized as a significant step in the successful colonization of the intestinal, respiratory and genito-urinary tracts in the early stages of infection. The attachment and agglomeration of organisms is important, both in the pathogenesis of infection and in limiting the response to antibiotic treatment.
>
> **Taurolidine has been found to significantly reduce the adherence** of buccal and vaginal isolates of candida albicans blastospores and urine isolates of escherichia coli and staphylococcus saprophyticus **to *epithelial cells*. Light microscopy and radio-isotopic counting methods were used to quantify the adherence of the microorganisms to** either uropithelial or buccal ***epithelial cells*.**
>
> **Treatment of either *epithelial cells* or microorganisms with taurolidine resulted in reduced adherence of microorganisms.**
>
> Using a thirty minute contact time, **a range of taurolidine concentrations** on the order of 0.05% to about 2.0% w/v **were examined for antiadherence activity. Significant decreases in** candida blastospore **adherence were observed** at concentrations of less than 0.1% w/v taurolidine. Maximum reductions in adherence, on the order of about 65% of control were observed when concentrations of taurolidine greater than about 0.5% w/v. Increasing the taurolidine concentration beyond this level did not produce a concomitant increase in antiadherence activity. Conversely, dilution of taurolidine concentration may proceed to a considerable extent before its capacity for antiadherence is lost.
>
> **The foregoing demonstrates that taurolidine exerts an antiadherence activity via a chemical modification of the outer surface structures such as fimbriae causing agglutination or disappearance of the structures**. The effect of taurolidine on these structures which contribute to the initiation of infection and in determining the pathogenicity of the organism is clear evidence of one aspect of taurolidine's mechanism of action in preventing infection or reducing its severity." (Specification pages 9 & 10, emphasis added).

It is the Office that bears the initial burden of showing that the claimed invention is not described in the specification. In re Wertheim, 541 F.2d 257, 265, (C.C.P.A. 1976). Furthermore, "[i]t is not necessary that the application describe the claim limitations exactly, In re Lukach, supra, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that [applicants] invented processes including

those limitations." Id., at 262. Obviously, the Examiner's suggestion that the specification is bereft of reference to "epithelial cells" was ill-founded. Moreover, Applicant submits that the above selection, clearly evincing an *actual reduction to practice*, would convey with reasonable clarity to those skilled in the art that, at the time of filing, Applicant was in possession of the invention. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

The Rejection of Claims 7 & 9 under 35 U.S.C. §102(b) in view of *Blenkharn*

Claims 7 & 9 have been rejected under 35 U.S.C. §102(b) as being anticipated by Blenkharn (Surg. Res. Comm., 1987, Vol. 2, pp. 149-155, hereinafter "Blenkharn"). Applicant submits that Blenkharn fails to disclose corresponding structure and therefore does not anticipate independent claim 7 or dependent claim 9. Blenkharn's abstract—the only part of Blenkharn cited for this portion of the rejection—discloses tauroldine's ability to prevent adhesion of micro-organisms to "epithelial *surfaces*." However, it is the reduction in adherence of microorganisms to "epithelial *cells*," with which independent claim 7 is concerned—not epithelial surfaces. Indeed, the disclosure is rather specific:

> "**taurolidine exerts an antiadherence activity via a chemical modification of outer surface structures such as fimbriae causing agglutination or disappearance of the structures**. The effect of taurolidine on these structures which contribute to the initiation of infection and in determining the pathogenicity of the organism is **clear evidence of one aspect of taurolidine's mechanism of action** in preventing infection or reducing its severity."

Furthermore, it is the specific reduction of the adherence of *urine* isolates of escherichia coli with which dependent claim 9 is concerned. *Urine* is nowise mentioned in Blenkharn, in fact Blenkharn only characterizes its strains as "*clinical* isolates," without

further designation. (p. 150). To the extent Blenkharn fails to disclose the above-discussed structural elements, Blenkharn fails to anticipate claims 7 and 9.

The Rejection of Claims 7-9, 11 and 12 under 35 U.S.C. §102(b) in view of *Gorman*

Claims 7-9, 11 and 12 have been rejected under 35 U.S.C. §102(b) as being anticipated by Gorman et al. (Journal of Pharmacy and Therapeutics, Vol. 12, pp. 393-399, (1987) hereinafter "Gorman"). Applicant submits that Gorman fails to disclose corresponding structure and therefore does not anticipate independent claim 7, or any of dependent claims 8, 9, 11, and 12. Gorman's abstract—the only part of Gorman cited for this portion of the rejection—discloses that taurolidine exhibits anti-adherence activity in two *specific* adherence systems. The first is one wherein the microorganism is an *oral* isolate of *Candida albicans* and the epithelial cells are *human buccal* epithelial cells. The second is one wherein the microorganism is a *urine* isolate of *Escherichia coli* and the epithelial cells are *human uroepithelial* cells. Independent claim 7 is not so restricted; its elements are drawn to *microorganisms* and *epithelial cells* in the broadest and most generic sense of those terms. Its microorganisms element is not limited to *oral isolates of Candida albicans* (Gorman system 1) or *urine isolates of Escherichia coli* (Gorman system 2). Nor is its epithelial cells aspect limited to *human buccal epithelial cells* (Gorman system 1) or *human uroepithelial cells* (Gorman system 2). Accordingly, neither of Gorman's adherence systems anticipates independent claim 7.

Gorman is equally uninstructive on the structural aspects of dependent claims 8, 9, 11, and 12. The elements of dependent claim 8 clearly contemplate an adherence system, wherein the microorganisms are *buccal* and *vaginal* isolates of *candida albicans*

blastospores—not the single and *oral* isolate of Gorman's first adherence system. Accordingly, neither of Gorman's adherence systems anticipate dependent claim 8. The elements of dependent claim 9 clearly contemplate an adherence system, wherein the microorganisms are *urine isolates of escherichia coli* and wherein the epithelial cells comprise as broad spectrum as those embodied in independent claim 7. The epithelial cells of claim 9 are not restricted to the *human uroepithelial cells* of Gorman's second adherence system. Accordingly, neither of Gorman's adherence systems anticipate dependent claim 9. The elements of dependent claim 11 conceive of an adherence system, wherein the epithelial cells are only limited insofar as they are *uroepithelial cells.* These uroepithelial cells are not necessarily *human* uroepithelial cells as disclosed by Gorman's second adherence system. And claim 11's microorganism component comprises as broad spectrum as those embodied in independent claim 7; similarly, it is not restricted to the *urine isolates of Candida albicans* of Gorman's second adherence system. Accordingly, neither of Gorman's adherence systems anticipate dependent claim 9. The elements of claim 12 conceive of an adherence system wherein the microorganisms component is as broad as claim 7—not limited to either of Gorman's *oral isolate of Candida albicans* or *urine isolate of Escherichia coli.* The only restriction on the method of claim 12 is that its epithelial cells are *buccal*—but not necessarily *human buccal*, as disclosed by Gorman's second adherence system. Therefore, neither of Gorman's adherence systems anticipate dependent claim 12.

The Rejection of Claim 10 under 35 U.S.C. §103(a) over *Gorman* in view of *Blenkharn*

The Office Action further rejected dependent claim 10 under 35 U.S.C. §103(a) as being unpatentable over Gorman in view of Blenkharn. That rejection is hereby traversed.

There are three basic requirements for the establishment of a *prima facie* case of obviousness. MPEP § 706.02(j). First, there must be some *motivation or suggestion* in the prior art reference itself, or in the knowledge generally available to one of ordinary skill in the art, *to modify* the reference *or to combine* its teachings with that of another. Second, there must be a *reasonable expectation of success*. This motivation/suggestion to modify/combine a reference(s) and its attendant reasonable expectation of success must both be founded in the prior art reference(s); they cannot be based upon the applicant's disclosure. In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991). Furthermore, if the reference(s) does not *expressly* or *implicitly* suggest the claimed modification/combination, the examiner must present a *convincing line of reasoning*[2] as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the reference(s). Ex parte Clapp, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985). Lastly, the prior art reference/s, once modified or combined, *must teach or suggest all the limitations* of the claims.

The primary reference, Gorman, fails to support a *prima facie* case of obviousness. As discussed above and as referred to in the rejection Gorman discloses

[2] The level of skill in the art cannot be relied upon to provide the suggestion. Al-Site Corp. v. VSI International Inc., 174 F.3d 1308, 1324 (Fed. Cir. 1999). To substitute the level of ordinary skill for motivations not found in prior art references is to engage in impermissible hindsight, "wherein that which only the inventor taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

"two adherence systems," "an oral isolate of *Candida albicans* to human buccal epithelial cells and a urine isolate of *E. Coli* to human uroepithelial cells" (Office Action page 5). Gorman makes no mention of *Staphylococcus* microorganisms of *any kind* let alone the *saprophyticus* variety as herein claimed. Gorman in no way suggests *Staphylococcus*, either expressly or implicity. And therefore, at the time Dr. Costin conceived claim 10, the artisan would not have viewed the modification of Gorman to a *Staphylococcus* adherence system as having a reasonable expectation of success. To the extent Gorman fails to teach or suggest the element of *Staphylococcus* in general, and to such further extent fails to teach the element of *Staphylococcus saprophyticus* in particular, Gorman fails to render claim 10 obvious.

The secondary reference, Blenkharn, does nothing to cure the deficiencies of the primary reference. Contrary to the rejection's assertions it is *not* noted in either reference that "treatments used against *Staphylococcus aureus* (which is mentioned in the Blenkharn reference) are also effective against *Staphylococcus saprophyticus*," (Office Action page 5). If the behavior of *Staphylococcus* as a general genus were as predictable as the rejection asserts one wonders why Blenkharn felt the need to use **50** separate strains of its *aureus* subgenus in his taurolidine research:

> "For initial screening of potential drug interaction, paper discs containing 5 mg taurolidine were used in a conventional comparative disc susceptibility testing technique. One hundred isolates of aerobic or facultative Gram negative bacilli, **50 strains of *S. aureus***, 15 strains of *Streptococcus faecalis* and 20 strains of Gram negative anaerobic bacilli were tested against appropriate antibiotics." (Blenkharn, p. 151, emphasis added).

Clearly, no generalism with regard to *Staphylococcus* and taurolidine is to be gleaned from Blenkharn alone, much less would the artisan extrapolate one from the further

teaching of Gorman which doesn't even mention *Staphylococcus*—let alone its *saprophyticus* subgenus as herein claimed. Accordingly, at the time the present invention was made, the artisan of ordinary skill relying on the teachings of Gorman and Blenkharn would not have viewed their combination / modification as having a reasonable expectation of success. The rejection fails to cite motivation because such motivation is found only through resort to impermissible hindsight and reference to the disclosures of the instant invention. The references do not teach or suggest the treatment of the *Staphylococcus saprophyticus* microorganism, and the rejection impermissibly marginalizes this distinction as being *obvious to try*. However Dr. Costin may have come to appreciate the aspects of dependent claim 10, its "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a). Whether a particular modification / combination might be "obvious to try" is not a legitimate test of patentability. In re Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987).

There is ample antecedent support for the above amendment. Both the instant specification and its provisional parent disclose the 1,1 dioxo functionalized nature of taurolidine. *See instant specification page 3, lines 7-9; provisional parent illustration page 2.* The compound's *tetra*hydro- aspect is disclosed in the instant specification at line 9 of page 2. The compound's ability to reduce the adherence of microorganisms to epithelial cells is discussed at length on pages 9 and 10.

In view of the foregoing, Applicant submits that the hereby-amended claims (7-12) are patentable in view of the cited references. Applicant additionally submits that

newly-added claims (13-17), each directed to further aspects of the invention are also patentable in view of the cited references. Applicant finally submits that the application is in condition for allowance, and he therefore requests its prompt passage to issue.

It is believed that no fee is due. However, if any fee is due it should be charged to Deposit Account No.: 03-0678.

CERTIFICATE OF MAILING

Deposit Date: June 12, 2002

I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service with sufficient postage as First Class Mail to Addressee, under 37 CFR 1.8, on the date indicated above addressed to:

Commissioner of Patents and Trademarks
Washington, DC 20231

6/12/02

Raymond E. Stauffer, Esq. **Date**

#144059 v1 - amendment & remarks

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[ABSTRACT]ABSTRACT OF THE DISCLOSURE

The use of 4,4-methylenebis (tetrahydro-1,2,4-thiadiazine-1,[2]1-dioxide) in the prevention and control of the development of antibiotic drug resistance in bacteria, [and] in the prevention of bacteria-to-bacteria transfer of genes capable of resisting antibiotics, and in reducing the adherence of microorganisms to epithelial cells is disclosed.

"Version with markings to show changes made." M.P.E.P §714

Specifically, the present invention relates to the use of 4,4'-methylenebis(tetrahydro-1,2,4-thiadiazine-1,1[2]-dioxide) known generically as taurolidine to treat antibiotic drug (e.g. gentamicin, vancomycin) resistant bacterial infections, nosocomial infections and/or eradication of these organisms from an individual acting as a "carrier" for these organisms.

"Version with markings to show changes made." M.P.E.P §714

7. (amended) A method for reducing the adherence of microorganisms to epithelial cells which comprises treating the microorganisms or epithelial cells with 4,4'-methylenebis([per]tetrahydro-1,2,4 thiadiazine-1,1-dioxide).